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EXAMINER	
BERCH, MARK L	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,141	ECKHARDT ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/23/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10,12,14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,10,12,14,16 and 17* is/are rejected.

7)☒ Claim(s) *2-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Structure III has been stranded at the end of claim 14; it needs to be canceled as the rest of the surrounding material was.
2. In claim 8, a proper composition claim must have a carrier of some kind; otherwise it is identical with a compound claim. Adding the carrier back will resolve the matter.

Claims 1, 10, 12, 14, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The indentations have not been handled properly. On page 3 of 39, there is :

i. R10 denotes

a. .....

b.....

This continues properly through t. However, u. is not a choice for R10 at all, but the start of something entirely new, the definition of R11 and R12. That is, what is designated as u. should actually be ii. That is ,v. should be iii, etc.

Claims 10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 10 language of "disease or condition associated....." is unclear. The scope of this is unknown. There is no standard list of such disorders. Creating such a list would be a colossal medical undertaking, and thus would constitute undue experimentation. Note that this claim language covers a) a disease or condition which causes the increased DPP-IV activity, b) a disease or condition which is caused by the increased DPP-IV activity, and c) a circumstance where the disease or condition and the increased DPP-IV activity are both caused by some other condition/disease, thus providing an association, and d) a disease or condition which appears to be correlated with the increased DPP-IV activity, but the nature of the connection is unknown. The examiner notes that the expression of DPP-4 (CD26) is regulated by the differentiation and activation status of immune cells (notably, resting T cells at low density), and therefore, anything which affects this would potentially be associated with an increase in DPP-4.

Claim 16 has a similar problem. There is no way of knowing what diseases this includes. Claim 16's scope is, however, somewhat different. This diseases/condition does not have to involve increased DPP-4 activity at all. Thus, this would cover disorders whose treatment involves suppressing DPP-4 from a normal level down to a subnormal level. Determining

which disease will really be preventable or alleviable is no simple matter. Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not

themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of claims 10 and 16 will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the huge scope of the 4 primary variables, the claims cover trillions of compounds.

(b) Scope of the diseases covered.

A. Claims 10 and 16 do not specifically recite treatment of disease. However, the only reason to give a person a medicinal in an amount effective to treat or prevent a disease is to treat or prevent the disease. Accordingly, the claim is presumed to include the treatment of disease. On the other hand, applicants removed the word "treating" from claim 10, implying that either a) treating is no required or b) the claim is not limited to treating.

B. As noted in the previous rejection, there is no way of knowing what the scope of the diseases are.

C. Using this specification, and also the teachings of 20040122228 (which has common inventors and was filed approximately the same time) as guidance, it lists the following: type 1 and type 2 diabetes mellitus, diabetic complications (such as e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation, calcitonin-induced osteoporosis, preventing B-cell degeneration (such as e.g. apoptosis or necrosis of pancreatic B-cells), improving or restoring the function of pancreatic cells, increasing the number and size of pancreatic B-cells, a sedative or anxiety-relieving effect favorably affecting catabolic states after operations or hormonal stress responses, reducing mortality or morbidity after myocardial infarct, as diuretics, as antihypertensives, for preventing and treating acute renal failure, inflammatory diseases of the respiratory tract, chronic inflammatory

intestinal diseases (e.g. irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis), pancreatitis, damage to or impairment of the gastrointestinal tract (such as colitis and enteritis), infertility, treating deficiencies of growth hormone which are associated with reduced stature, autoimmune diseases (e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease), viral diseases (e.g. HIV infections), for stimulating blood production, benign prostatic hyper-plasia, gingivitis, neuronal defects and neurodegenerative diseases (such as Alzheimer's disease), treatment of tumours (particularly for modifying tumour invasion and also metastasisationsuch as treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based pancreatic carcinomas, basal cell carcinomas or breast cancers), stroke, ischaemia of various origins, Parkinson's disease, migraine, follicular and epidermal hyperkeratoses, increased keratinocyte proliferation, psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds. A few of these categories are discussed as follows:

D. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders, or disorders generally considered to be autoimmune include Polymyositis, Scleroderma, Osteosclerosis, Meniere's disease, Idiopathic neutropenia, Idiopathic thrombocytopenic purpura, Autoimmune hemolytic anemia, Premature ovarian failure, Idiopathic hypoparathyroidism, primary biliary cirrhosis, Pemphigus, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré

syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behçet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Autoimmune Atherosclerosis and many more.

E. The scope inflammatory diseases of the respiratory tract is quite broad. Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes. Sinusitis is the arises from the infection of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma

to the nose, and foreign objects that are stuck in the nose. Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers. Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation. Pulmonary Emphysema is a chronic lung condition with a significant inflammatory component, in which alveoli (air sacs) may be destroyed, narrowed, collapsed, stretched or over-inflated. Pulmonary emphysema occurs when a breakdown in the chemical balance that protects the lungs against the destruction of the elastic fibers occurs. This can arise from smoking, exposure to air pollution, irritating fumes and a rare, inherited form of the disease, called alpha 1-antitrypsin (AAT)deficiency-related pulmonary emphysema, or early onset pulmonary emphysema. Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis) is a term that includes more than 180 chronic lung disorders, which may be

chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness. There are many Occupational Lung Diseases, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors). Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections

(lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs. Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral

medications, inhaled medications, immunotherapy, and surgery for some conditions. There are many others.

F. The term "neurodegenerative disorders" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; dementia of the frontal lobe type (DFT) and DFT with motor neuron disease (DFT-MND); Diffuse Lewy Body Disease; Cortical Lewy body disease; Hallervordon-Spatz disease; Senile dementia of the neurofibrillary tangle type ("tangle-only dementia"); progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; more than a dozen dementias collectively called "frontotemporal dementia" (FTD); Tourette's syndrome; multiple systems atrophy (MSA; once called Shy-Drager syndrome), which exists in two forms: MSA-P type or MSA-C type; Neurological syphilis; Neurosarcoidosis; Pure autonomic failure (Bradbury-Eggleston syndrome); Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); ophthalmic disorders such as primary open-angle glaucoma (POAG) and retinitis pigmentosa; Leber's Disease; Wallerian degeneration, assorted prion diseases, and Hypertrophic interstitial polyneuropathy. There is the neuroacanthocytosis family, a difficult to define group of genetic disorders which includes Bassen-Kornsweig disease (abetalipoproteinemia), Familial hypobetalipoproteinemia, Chorea-acanthocytosis (ChAc), McLeod syndrome (MLS) , Huntington disease–like2

(HDL2) and Pantothenate kinase–associated neurodegeneration (PKAN), FHBL1, FHBL2, Familial acanthocytosis with paroxysmal exertion-induced dyskinesias and epilepsy (FAPED), and Anderson disease. There is a group of Prion diseases, notably Creutzfeldt-Jakob Disease (CJD), which occurs in both sporadic and familial forms; Gerstmann-Straussler-Scheinker Disease (GSS); and fatal familial insomnia. There is another group called the Taupathy diseases, which includes Pick's disease; cortical-basal ganglionic degeneration (CBGD or CBD); progressive supranuclear palsy (PSP); Parkinsonism-dementia complex(PDC), and the amyotrophic lateral sclerosis/Parkinsonism-dementia complex(ALS-PDC). Another group is the Polyglutamine diseases: Huntington's disease; spinal-bulbar muscular atrophy (Kennedy's disease or SBMA), Dentatorubral-Pallidoluysian Atrophy (DRPLA), Machado-Joseph disease (MJD, also called spinocerebellar ataxia type 3), and the other SCA diseases, viz SCA-1, SCA-2, SCA-6, and SCA-7. Neurodegeneration can arise from the attack of unknown viruses on the brain, from stroke, and from certain types of spinal cord injuries. These exhibit a very broad range of effects and origins. For example, some give no dementia and affect only vision, such as POAG. Some give progressive dementia without other prominent neurological signs, such as Alzheimer's Disease, whereas other dementias do have such signs, such as Diffuse Lewy Body Disease. Many give distinctive and different patterns of effect. For example, FTDs, which have bilateral atrophy of the frontal and anterior temporal lobes, produce progressive nonfluent aphasia and semantic dementia, but, in contrast to e.g. Alzheimer's Disease, visuospatial skills and day-to-day memorizing is largely unaffected. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some affect only vision such as retinitis pigmentosa,

while others affect both vision and cognitive functions, such as Posterior cortical atrophy (PCA). Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some give an extremely broad range of effects. For example, CBD can give apraxia, alien limb phenomenon, cortical sensory loss, aphasia, myoclonus, bradykinesia, rigidity, dystonia, tremor, memory impairment and/or personality/behavioral changes. The toxic protein involved also varies. In some cases it is tau, especially Alzheimer's Disease and Taupathy, and some are so linked to tau only sometimes (FTD). Alzheimer's Disease also involves ß-amyloid. For Parkinson's disease it is α-synuclein, while ALS is linked to SOD1. Prion disease involves PrP^{Sc} as its toxic protein, which involves missense. The polyglutamine diseases involve polyglutamine containing proteins. For Huntington's disease, it is huntingtin, for SBMA it is an androgen receptor, for DRPLA it is atrophin, for SCA-1 it is Ataxin-1, for SCA-2 it is Ataxin-2, for SCA-3 it is Ataxin-3, for SCA-6 it is calcium channel protein, and for SCA-7 it is Ataxin-7. The nature of the protein deposits varies as well. In Alzheimer's Disease, there are extracellular plaques from ß-amyloid and neurofibrillary tangles (from tau). In Parkinson's disease it is Lewy bodies and in ALS it is Bunina bodies. Taupathy produces cytoplasmic tangles, and Polyglutamine disease produce neuropil aggregates, intranuclear inclusions and cytoplasmic tangles. Prion disease produces prion plaque. And note that the disease form is not necessarily related to the protein deposits. For example, Alzheimer's Disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's Disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's Disease.

The disease genes vary considerably as well. In Alzheimer's Disease, there is toxic gain of function with APP and loss of function of Presenilin 1 and presenilin 2. With Parkinson's disease, there is toxic gain of function with α-synuclein, and loss of function of Parkin and UCHL1. In the Polyglutamine diseases, there is toxic gain of function with 9 different genes with CAG repeat expansion. In Prion disease, there is toxic gain of function with PRNP. In ALS there is toxic gain of function with SOD1. FTDP-17 arises from mutations at chromosome 17, Huntington's Disease from chromosome 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to chromosome 21.

G. Treatment of tumors cover all cancers except for leukemias and certain lymphomas whicha re not tumors. Further, "tumor" covers more than just cancers. It also covers many neoplasms, cancerous or not. A neoplasm is any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term, also covers precancerous conditions such as lumps, lesions, and polyps. In addition, "tumor" covers things other than neoplasms. It also covers any kind of swelling arising from inflammation. As was noted in *Ex parte Aggarwal*, 23 USPQ2d 1334, 1336: "In its broadest reasonable sense, the term "tumor" designates any tumor, whether malignant or benign." Thus, the claim would cover treatment of many kinds of inflammation which produce tumors which are not malignant.

H. The phrase "psychosomatic, depressive and neuropsychiatric diseases of all kinds" would cover most serious mental disorders, including depression, psychosis, bipolar disorders, delirium, etc..

I. Viral diseases would cover any virus. There are thousands of viruses.

J. The term "arthritis" is used for any kind of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-I and IFN-K. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown, and the full mechanism has not been discovered. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from RA. There are also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to prevent viral infections), fungi, or parasites. Included in this category are various types of septic arthritis and mycotic arthritis, and

viral arthritis, such as rubella arthritis, Lyme arthritis, Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by Chlamydia trachomatis) etc. These assorted disorders can arise from quite varied sources. Thus, in addition to the above, CPDD, sometimes called pseudoosteoarthritis, or pseudogout, arises from Calcium Pyrophosphate Deposition. Menopausal arthritis is due to ovarian hormonal deficiency. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. Arthritis can also arise from injury to the supporting ligaments or other structures contained within or associated with the joint, a condition often called post-traumatic arthritis. These various forms of arthritis are so diverse that no one form can be considered as representative of "arthritis" as a whole.
(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 37 is incomplete, in that it is given in the form of mg, not mg/kg. Moreover, this is generic, the same for the many disorders covered by the specification, which are quite

extensive. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for this or that disease.

(4) State of the Prior Art: These compounds are 7-substituted xanthines with a particular substitution pattern at the 1-, 3- and 8-positions. So far as the examiner is aware, no 7-substituted xanthines of any kind have been used for the treatment of e.g. arthritis, Alzheimer's Disease, brain tumors, migraine, rheumatoid arthritis, multiple sclerosis, Parkinson's disease, Crohn's disease, etc.

(5) Working Examples: There are none, and indeed, there is no biological data of any kind.

(6) Skill of those in the art: This varies greatly according to the disorder. Here are some examples:

I. There are huge differences in origins of neurodegenerative disorders, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are clearly different, since different genes are involved. Many, e.g. neurosarcoidosis, are of unknown origin. The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with agents such as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of so many compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the

massive research effort on Alzheimer's Disease has produced are means of providing Acetylcholinesterase inhibition, (Aricept®, Cognex®, Exelon®, and Reminyl®), or voltage-dependent NMDA-antagonists (Memantine), properties these compounds are not disclosed to have.

II. The skill level in respiratory inflammatory disorders varies considerably. In many cases, the only real treatment is to attack the infectious organism which caused the problem in the first place, e.g. be an antibacterial, a property which these compounds are not disclosed to have. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

III. The skill level in Rheumatoid Arthritis is relatively low. Very few agents have been successfully used to treat RA itself, and these have all operated by the mechanism of α-TNF inhibition. There has been some research on the use of DPP-IV inhibitors for RA, but even as of 2005, after the instant filing date, the situation is still unclear. Moreover, some early positive results have recently been reassessed. In Busso et al., American Journal of Pathology 166:433-442 (2005), it is stated: "Paradoxically, although DPPIV inhibition was beneficial in experimental models of RA and multiple sclerosis, genetic deficiency of CD26 leads to exacerbation of these diseases: AIA was more severe in CD26-deficient mice (this study); similarly, EAE was exacerbated in CD26-knockout mice. The reasons for such discrepancy may be related to the additional effects of the inhibitors, able to act even in DPPIV-deficient animals suggesting that, besides DPPIV inhibition, these inhibitors may have other functional targets." In other words, the beneficial effects seen in earlier studies are likely not to have arisen from DPPIV inhibition, but from the fact that the particular

drugs used had "other functional targets." In particular, the paper goes on to suggest that the other target may be DPP8/9, i.e. that the drugs were not particular selective for DPP-IV. Thus, it is clear that, even as of 2005, it has not been established that inhibition of DPP-IV is of value in treating RA, and indeed, such a conclusion is inconsistent with the fact that AIA was more severe in CD26-deficient mice. With regard to the skill in the art of the treatment of the other forms of arthritis, there is no one single pattern. For example, Acute attacks of gouty arthritis are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis is treated with NSAIDs and COX-2 inhibitors. CPDD is treated with nonsteroidal anti-inflammatory drugs, corticosteroids and Colchicine. Neuropathic arthritis is approached by trying to remove the source of the toxin, but cannot always be treated per se. Infectious arthritis is dealt with by treating the underlying infection, when possible. Treatment of arthritis generally has never been accomplished, and, owing to the extremely diverse mechanisms by which this can occur, there is no reason to think that this can be accomplished.

IV There are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic

lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis.

3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have

been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

V. Many categories of tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. Pilocytic astrocytoma and Diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs. Cartilage tumors do not respond to chemotherapy, nor do Cancerous teratomas. Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones. Neuroendocrine tumors of the cervix generally do not respond to chemotherapy. Renal cell carcinoma does not respond to chemotherapy. A number of sarcomas, including Alveolar soft part sarcoma (ASPS),

retroperitoneal sarcoma, most liposarcomas (see claim 9), and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no chemotherapeutic agent has been established as effective. Many cerebral metastases, such as those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy. Hepatocellular Carcinoma is, in humans, possibly the most prevalent solid tumor. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer.

VI. IBD arises from a ranges of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, for example are idiopathic. Ischaemic Colitis arises from partial death of tissue (infarct) due to blockage in the blood supply, e.g. after major abdominal surgery or poor cardiac output in heart disease. Radiation enterocolitis arises from chemotherapy of cancer. Infective Colitis can arise from bacteria (e.g. Shigella, Salmonella, Campylobacter, E. coli) or Viruses (e.g. Norwalk-like virus rotavirus, CMV and HSV). Diversion Colitis develops from the diversion of the faecal stream following colostomy or ileostomy. Treatment depends on form, and some, such as radiation enterocolitis and SRUS, have no effective pharmaceutical treatment.

VII. The skill level in PD is very low relative to the difficulty of task. Parkinson's Disease is a neurodegenerative disorder which, like most neurodegenerative disorders, has been highly resistant to pharmaceutical treatment. The disease is characterized by the degeneration and death of dopamine-producing cells in the substantia nigra, located in the midbrain, along with the presence of cytoplasmic protein inclusions called Lewy bodies. PD is considered to be a cluster of related disorders. The majority of cases of PD are deemed sporadic, but there are also familial forms of PD. This death is of unknown origin

(idiopathic), and cannot itself be stopped. Current drug regimens for Parkinson's disease are aimed instead at symptomatic relief, primarily through a dopaminergic effect. This includes dopamine replacement therapy (L-dopa), COMT inhibitors (which facilitate the conversion of L-Dopa to dopamine itself), Amantadine (which appears to increase dopamine synthesis in the remaining cells), dopamine agonists (which mimic dopamine) or MAO B inhibitors (e.g. Selegeline which reduces or delays the breakdown of dopamine). These do not actually treat the disease itself, but instead seek to boost the amount of dopamine available by various mechanisms. At the time of filing, and indeed at present, no drug has been scientifically demonstrated to treat the disease itself, rather than provide relief for this or that symptom.

(7) The quantity of experimentation needed: Owing to the above, especially points 1, 3 ,4, 5 and 6, this is expected to be substantial.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 2-6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Berch
Primary Examiner
Art Unit 1624

3/21/07